Mamane: Scientific Therapy for Asthma?*

Douglas G. Massey MD,** Yu Kun Chien MD,†
Gisele Fournier-Massey MD, PhD††

Mortality from asthma in Hawaii continues to increase and chronic problems of medication compliance, side effects, and cost persist. The advisability of adding alternative (traditional) medication for its anti-inflammatory and anti-allergic function was examined. One of the herbs for asthma in the Hawaiian narrative tradition is mamane, or in scientific terminology, Sophora chrysophylla. The scientific literature on S. chrysophylla and of the closely related species Sophora flavescens ait were reviewed in this context and the findings support further investigation.

Introduction

Mortality from asthma has increased in Hawaii since the 1980s and still shows no consistent decline.[1] Furthermore, compliance with therapy, drug side effects, and costs continue to be chronic problems. To determine the potential contribution of alternate medicine to their resolution, a historical review of written and traditional narrated Hawaiian materia medica for asthma was conducted and 58 herbs were selected as being potentially useful therapeutically.[2] Among these was *mamane* or *Sophora chrysophylla*.

We selected *S. chrysophylla* for a scientific literature review of its role in asthma. In addition to its local use, the genus *Sophora* has been a source of alternative medication for centuries for people from India to America.[3] The structurally similar *Sophora flavescens ait* (*SFA*) has extensive scientific literature.

Methods

The scientific literature was searched under the headings of *mamane* and of *S. chrysophylla*. Subsequently, the search centered on the scientific bibliography of the closely related species, *Sophora flavescens ait*.

* Department of Immunology, Beijing Medical University; Pulmonary Services, Kuakini Medical Center, Honolulu and Department of Medicine, John A. Burns School of Medicine, University of Hawaii.
** Visiting Professor of Medicine.
† Professor of Immunology, Beijing Medical University.
†† Visiting Senior Research Associate.

Reprint requests to:
Professor Chien
Department of Immunology, Beijing Medical University
38 Xue Yuan Lu, Beijing, 100083, People's Republic of China.

Results

Botany

Leguminosae or the pea family is the third-largest family of flowering plants, consisting of some 600 genera and 17,000 species.[4] It has 3 subfamilies, one of which is *Papilionatae*, and it contains the genus *Sophora*. Among the 50 or so species of *Sophora* are *S. chrysophylla* and the closely related *SFA*. The former is endemic to Hawaii,[5] and the latter is found in China.[6a]

The growth of *mamane* varies from a shrub at low altitudes to a tree 2 feet in diameter and 40 feet tall at high altitudes.[7] It is widespread except on the island of Molokai. Optimal growing conditions include sunny slopes, heavy rainfall, and strong winds.

Although flowers, leaves, seeds and bark have medicinal properties, the root is the portion used most frequently; it is believed to be best harvested with appropriate religious ceremonies.

Chemistry

A century ago, chemists investigated the subfamily *Papilionatae* because of its poisonous side effects when used as cattle fodder, as applications in veterinary medicine, and as insecticides.[8] The major components are alkaloids with some flavonoids, glycoproteins, and chromones.[6a,9]

Alkaloids are nitrogen-containing compounds widely used medicinally. The alkaloidal content and structure of *S. chrysophylla* have been investigated.[8,10-13] Among these were anagyrine, cytisine, mamanine, matrine, pohakuline, sophochrysine, and sophoramine. Major alkaloids of the closely related species, *SFA*, are anagyrine, baptifoline, cytisine, matrine, N-methylcytisine, oxymatrine, sophocarpine, sophoramine, and sophoranol.[14] Their biogenesis has been extensively studied with isotope tracers.

Quantitatively and qualitatively matrine, or $C_{15}H_{24}N_2O$, is the major alkaloid of these 2 species. Attention also is drawn to oxymatrine, $C_{15}H_{24}N_2O_2$, which is structurally almost identical and has the same solubility profile.[6a] Matrine is easily oxidized by H_2O_2 to oxymatrine which, in turn, is reduced to matrine by hydrogen. The extensive international research literature on oxymatrine may be applicable to matrine.

Absorption, fate, and excretion

S. chrysophylla is traditionally administered either as a tea or topically[15] and other *Sophoras* are available in the form of tablets, aerosols, and intramuscular and intravenous preparations.[3] No data is available on the metabolism of *S. chrysophylla*, but research has been published on those components it shares

with the closely related *Sophora* species.

Oral matrine was absorbed in rats and mice and was widely distributed in tissues with selective concentration in the lungs; for this reason, matrine may be more suitable than other alkaloids of *Sophora* in the therapy of asthma.[16] In rats, 80.1% of ingested matrine was excreted in the urine in less than 24 hours, and in humans, 60%.

Oxymatrine was metabolized somewhat differently than matrine, depending on the route of administration. Oral oxymatrine was transformed to matrine in the gastrointestinal tract of rats and mice, which explains why the concentration of matrine was higher than oxymatrine in the tissues. By 24 hours, 80% of the oxymatrine ingested was excreted, more as matrine than oxymatrine.[16] In 3 humans who took 380 μM of oxymatrine orally at night, the total combined matrine and oxymatrine found in the urine in 24 hours was 41.1%, 43.2%, and 70.1%, respectively, and of these 67.1%, 61.1%, and 53.1% was matrine.[16] When given intramuscularly, oxymatrine concentration was high in tissue, bile, and urine with 85.3% of the total dose being excreted unchanged in the urine in 24 hours.[16] Intravenous oxymatrine in rats disappeared rapidly from the plasma with the plasma concentration versus time following a 2-compartment model: T 1/2 (a) = 5.8 min and T 1/2 (ß) = 27.0 min.[16] There was no prolongation of the half-life or elimination by increasing the dose by 25, 50, or 100 mg/kg intravenously. In a similar study in rabbits, oxymatrine was given intravenously as 25, 50, or 100 mg/kg.[17] The plasma concentration-time curves again fitted the 2-compartment model of 5.8 and 29.6 min respectively and pharmacokinetic parameters a and b were not changed with variable drug doses. Excretion was renal with little or none in the feces or bile.

Pharmacology

Bronchodilator.—*Sophora* alkaloids have an antiasthmatic effect.[3] As with theophylline, *Sophora* has influenced the activity of adenylate cyclase or phosphodiesterase,[18] but findings by Y.K. Chien in 1992 noted that the cAMP level remained stable with oxymatrine therapy and did not confirm in vitro a phosphodiesterase effect, at least with this alkaloid.

S. japonica agglutinin labeled the small mast cells but not the large[19] perhaps indicating a selective action of *Sophoras* on bronchodilation.

Anti-inflammatory.—The importance of inflammation in asthma has been stressed recently. Management of this chronic inflammation is difficult even with anti-inflammatory drugs such as steroids, methotrexate, and gold salts because of toxicity. The benign anti-inflammatory action of *Sophoras* could be utilized. There is extensive evidence of this function.[20-21] An effect of *SFA* was modification of interleukin-1 and interleukin-6 of inflammatory asthma.

Anti-allergy.—Matrine and oxymatrine have major anti-allergic actions. Using a model of immediate hypersensitivity in the guinea pig, oxymatrine decreased mortality to 61% and suppressed the IgE response ($p<0.01$) after a week of treatment.[22-23]

Histamine release from mouse peritoneal mast cells was suppressed by oxymatrine when it was induced by allergic stimulants anti-DNP IgE, and TNP-KLH, but not by non-allergic stimulants such as PMA, A23187, or ATP.[24] Oxymatrine might interfere with histamine release by stabilizing the mast cell membrane and decreasing its fluidity in a dose-dependent manner.

Immune response.—In 15 patients with severe asthma, 50% purified *SFA* administered over 2 months lowered IgE, but not IgA or IgG, and increased interleukin-1 and -4.

According to the Y.K. Chien, et al. studies, the concentration of Sophoras is a major determinate of their action on the immune system. Using lymphocyte numbers and interleukin levels as markers in mice, oxymatrine stimulated the immune system at low concentrations (10^{-5} to 10^{-2}) and suppressed it at higher concentrations (>1.0 mg/ml).

Among actions gleaned from the literature, *SFA* alkaloids inhibited antibody production in sensitized animals and depressed their skin reaction. Matrine inhibited the phagocytic function of mouse peritoneal macrophages in vitro.[19] Also, oxymatrine inhibits B but not T lymphocytes.[19,24]

Antibiotic.—Infection is a frequent trigger of asthma, and antibiotics are important for prophylaxis and for treating episodes. A 1% solution of matrine inhibited in vitro growth of such organisms as *Bacillus dysenteriae*, *Escherichia coli*, *Bacillus proteus*, *ß- streptococcus*, and *Staphlococcus aureus*. *SFA* solution inhibited violet mycelial fungus, several skin fungi, trichomonas, and influenced flagellae.[25]

Toxicity and Precautions.—After centuries of use, very little toxicity has been linked to *S. chrysophylla* or to *SFA*.[6b] Unlike allopathic medicine where the purity of a drug is paramount, alternative medication consists of a number of components that display a balance between active constituents and those that buffer the side effects. Thus, a desiccated root has few side effects, extracts have more, and purified products can rarely be seriously toxic.[3]

Of importance in asthma are the rare reports of presumed respiratory dysfunction. Matrine has been associated with respiratory center depression in animals, but the results are variable.[6b] When administered into rabbit ears intravenously, matrine up to 0.036 mg/kg was safe, 0.045 to 0.10 mg/kg led to weakness, 0.10 to 0.11 mg/kg could lead to failure with a partial recovery, but 0.133 mg/ kg led to signs of fear, limb weakness and spasm, and a respiratory death. In another study, the LD_{50} of intravenous matrine in rabbits was 125 mg /kg.[6b] In mice, it was 150 mg/ kg.[6b]

Oxymatrine showed an LD_{50} with 150 mg/kg intravenously given to mice and 750 mg/kg intra-peritoneally.[6b] Another study found values of 952.6 ± 11.6 mg/kg and 519 ± 15.18 mg/kg intraperitoneally, respectively.[6b] The LD_{50} for acute toxicity in mice was 256.74 ± 57.36 mg/kg and intravenously was 144.2 ± 22.8/ kg according to personal communication with Y.Y. Chen, Professor of Pharmacology at the Beijing Medical University in 1992.

Sophocarpine, another alkaloid, might slow respiration and decrease blood pressure when injected intra-peritoneally in rabbits in large doses, ie, up to 150 mg/kg or 78 ± 1.6 mg/kg.[6b]

In tests of mutagenicity, Yin found that *SFA* induced chromosomal aberration in *Salmonella typhimurium*[26] but this was not confirmed by Chen.

Clinical Applications

No controlled trials of *Sophora* in asthma or infective asthma have been published in Western medical literature. The Anti-asthma Drug Research Group, Department of Pharmacology at Guiyang Medical College reported that alkaloids of *SFA* used to treat 87 cases of chronic asthmatic bronchitis and 37 cases of bronchial asthma led to 90.3% success. Antitussive and expectorant actions were noted. A controlled, double-blind study was performed over 3 months in 15 severe asthmatics with 50% purified *SFA*. There was clinical improvement with increased tolerance to methacholine bronchial challenge, decreased use of

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steroids, a drop in IgE, and alteration to interleukins. The *SFA* was cost-effective compared to the pretrial use of medication.

Conclusions

Among the herbal therapies for asthma used in Hawaii for centuries is *mamane*, or *S. chrysophylla*. It has the potential for excellent patient compliance, clinical improvement, and few side effects at a low cost. A review of the known scientific facts of this medication supplemented by those of the closely related species, *SFA*, suggests that *mamane* should be further assessed. An extract of the root of *S. chrysophylla* of research quality should be prepared for suitable scientific research.

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